

<https://helda.helsinki.fi>

Predictors of New Airway Obstruction - An 11 Year's Population-Based Follow-Up Study

Vasankari, Tuula

2019-01-02

Vasankari , T , Harkanen , T , Kainu , A , Sääksjärvi , K , Mattila , T , Jousilahti , P & Laitinen , T 2019 , ' Predictors of New Airway Obstruction - An 11 Year's Population-Based Follow-Up Study ' , COPD: Journal of chronic obstructive pulmonary disease , vol. 16 , no. 1 , pp. 45-50 . <https://doi.org/10.1080/15412555.2019.1576163>

<http://hdl.handle.net/10138/308876>

<https://doi.org/10.1080/15412555.2019.1576163>

acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

1 Predictors of new airway obstruction - an 11 year's population based follow-up study

2

3 Tuula Vasankari, MD, PhD, Professor ^{1,2}

4 Tommi Härkänen, PhD ³

5 Annette Kainu, MD, PhD ^{4,5}

6 Katri Sääksjärvi, PhD ³

7 Tiina Mattila, MD, PhD ^{3,6}

8 Pekka Jousilahti, MD, PhD, Professor ³

9 Tarja Laitinen, MD, PhD, Professor ^{1,7}

10

11 ¹ University of Turku, Division of Medicine, Department of Pulmonary Diseases and Clinical
12 Allergology, Turku University Hospital and University of Turku, PO Box 52 (Hämeentie 11),
13 20521 Turku, Finland.

14 ² Finnish Lung Health Association (FILHA), Filha ry, Sibeliuksenkatu 11 A 1, 00250 Helsinki,
15 Finland.

16 ³ National Institute for Health and Welfare, PO Box 30, 00271 Helsinki, Finland.

17 ⁴ University of Helsinki, Department of Medicine, 00014 University of Helsinki, Finland.

18 ⁵ Terveystalo Healthcare, Jaakonkatu 3B, 00100 Helsinki, Finland.

19 ⁶ Department of Pulmonary Diseases, Heart and Lung Center, Helsinki University Hospital,
20 Meilahti Triangle Hospital, 6th floor, PO Box 372, 00029 HUS, Helsinki, Finland.

21 ⁷ Tampere University Hospital, Teiskontie 35, 33520 Tampere, Finland

22

23 **Corresponding author:** Tuula Vasankari, Finnish Lung Health Association (FILHA), Filha ry,
24 Sibeliuksenkatu 11 A 1, 00250 Helsinki, Finland. E-mail: tuula.vasankari@filha.fi, tel.: +358 50
25 5450589.

26

27

28 **Abstract**

29 In the present study we aimed to investigate the incidence and predictors of spirometry based
30 airway obstruction in a representative population-based sample.

31 Altogether 3863 subjects, 1651 males and 2212 females aged ≥ 30 years had normal spirometry in
32 year 2000. 53% of them were never and 23% current smokers. A re-spirometry was performed 11
33 years later. Several characteristics, such as level of education, use of alcohol, physical activity, diet
34 using AHEI index, BMI, circumwaist, sensitive CRP and cotinine of the laboratory values and co-
35 morbidities including asthma, allergic rhinitis, sleep apnoea and chronic bronchitis, as potential risk
36 factors for airway obstruction were evaluated.

37 Using FEV₁/FVC below the lower limit of normal, we observed 124 new cases of airway
38 obstruction showing a cumulative 11-year incidence of 3.2% and corresponding to an incidence rate
39 of 5.6/1000 PY. The incidence rate was higher in men than in women (6.3/1000PY vs. 5.0/1000PY,
40 respectively). The strongest risk factors were current smoking (OR 2.5) and previously diagnosed
41 asthma (OR 2.1). Sensitive CRP associated with the increased risk and high AHEI index with the
42 decreased risk of airway obstruction.

43 Using the similar study approach our findings on the incidence of airway obstruction are in line
44 with the previously published figures in Europe. We were able to confirm the recent findings on the
45 protective effect of healthy diet.

46

47 **Keywords:** COPD, airway obstruction, spirometry, incidence, healthy diet

48

49 **Introduction**

50 Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity, disability
51 and death worldwide [1, 2]. Based on a global estimate in 2010 the prevalence of COPD in adults
52 over 30 years of age was 11.4% being more prevalent among males (14.3%) than females (7.6%)
53 [3].

54 In studies on COPD incidence, two main approaches have been used. First, diagnosis based studies
55 have attempted to define COPD based on clinical outcomes such as outpatient contacts, hospital
56 visits for exacerbations, or self-reported physician diagnosed COPD. These studies have reported
57 incidence rates around 2.6–2.9 cases / 1.000 patient years (PY) with higher incidence rates found in
58 males and among older age categories [4,5]. The second approach is based on by showing
59 irreversible airway obstruction in spirometry. Furthermore, the definition of airway obstruction
60 varies [6-12]. Many epidemiological studies have used the Global Initiative on Obstructive Lung
61 Disease (GOLD) definition of a fixed ratio of forced expiratory volume in one second (FEV₁) to
62 forced vital capacity (FVC) below 0.70. Fixed ratio has the benefit of easy comparability between
63 populations, but is known to give false positives in subjects over 50 years of age. One example of
64 this is the Rotterdam study, the incidence was almost 50% lower when population based reference
65 values were used instead of the fixed ratio (5.5/1.000 PY vs. 8.9/1.000 PY), respectively [7]. There
66 is a large number of population based epidemiological studies that have evaluated the incidence of
67 airway obstruction based on fixed ratio with widely varying incidence rates, 2.8–16.0 /1.000 PY [7-
68 12]. Population age distribution, smoking habits and sampling differences can partially explain
69 these widely varying incidence estimates.

70 Smoking is the main causative factor for COPD [2], but also other -causative and predisposing -
71 factors have been recognised. Many of them are linked to low socioeconomic status [13],
72 occupational exposures [14] and old age [15]. Of studied biomarkers, sensitive C-reactive protein

73 shows the most constant association to low lung function and COPD [16]. Recently the diet has
74 become of great interest, especially the association between low vitamin D levels and declined lung
75 function [17], even though no causality to the incidence of COPD could be observed [18]. Also an
76 association has been observed between high consumption of processed meat and lower lung
77 function [19], whereas high fruit and vegetable consumption lowered the risk of COPD among
78 current and ex-smokers [20]. Lately, high Alternate healthy eating index (AHEI 2010) has been
79 associated with a lower risk of COPD [21].

80 The primary objective of this study was to investigate the incidence of airway obstruction in a
81 population with high standard of living and smoking steadily decreasing [22, 23]. Spirometry based
82 incidence on airway obstruction have never been published in Finland. The secondary objective was
83 to find out associative factors of development of airway obstruction.

84

85 **Methods**

86 A sample of 9922 subjects aged 18 years or over was drawn from the population register (two-stage
87 stratified, random sample) and invited to a comprehensive health survey (Health 2000 survey) in
88 2000-2001 [24]. Of these subjects, 8028 (3637 males and 4391 females) were aged 30 years or
89 over, and of whom altogether 6354 (79%) subjects completed the health examination, donated
90 blood samples, and performed spirometry.

91 All study subjects of Health 2000 survey who lived in Finland were invited to participate Health
92 2011 survey (n=8135 subjects), and 58.2% (4736/8135) of them completed the health examination.
93 The study population in the present study comprised of those 3863 subjects who were aged 30 years
94 or over in Health 2000, participated and performed spirometry in both Health 2000 and Health 2011
95 surveys and had normal spirometry in Health 2000 survey.

96 Our aim was to analyse how baseline data collected in Health 2000 survey predicted airway
97 obstruction in follow-up until Health 2011 survey. In Health 2000 survey information on age and
98 gender (female/male) were obtained from population register. Height, weight and circumwaist were
99 measured. Body mass index (BMI) ($\text{weight (kg)}/\text{height}^2 (\text{m}^2)$) was determined. The use of alcohol
100 during previous 12 months was determined and categorised as: no, seldom (use of alcohol twice in a
101 month or less) and often (use of alcohol once in a week or more often).

102 Smoking history was obtained through a standard interview and classified into three categories:
103 never-smokers (those who had smoked daily less than 1 year during their life-time and quit smoking
104 at least one month earlier), former smokers (those who had smoked daily over a year and quit
105 smoking at least one month earlier) and current smokers (those who had smoked daily over a year
106 and at least one cigarette, cigar or pipe for less than a month ago at any time preceding the survey).

107 Educational level was categorised into three groups (basic, secondary, or higher). Leisure physical
108 activity was classified into three groups: low (little physical exercise), moderate (exercise in
109 connection with some hobbies or irregularly), or high (regular exercise).

110 Subjects were considered asthmatic if they reported that they had been diagnosed with asthma by a
111 physician, that they were currently in a physician's control and received medication for asthma. The
112 history, symptoms and possible findings of allergic rhinitis, chronic bronchitis, and sleep apnoea
113 were inquired about in the basic questionnaire and categorised as having these or not.

114 Participants' habitual dietary intake over preceding 12 months was collected with a validated 128-
115 item semi quantitative food frequency questionnaire (FFQ) [25, 26]. Adherence to the healthy diet
116 was measured using the Alternate Healthy Eating Index (AHEI) developed by McCullough et al.
117 (2002) [27]. The AHEI in our data included the intake of seven components (vegetables; fresh fruits
118 and berries; nuts and legumes; rye; the ratio of white to red meat; the ratio of polyunsaturated to
119 saturated fat; trans fat), which were divided into sex-specific quintiles. The first six components

received scores in an ascending order, so that one point was assigned for intakes in the lowest quintile and five points for intakes in the highest quintile. The trans fats component received scores in the descending order, with the lowest quintile gaining a value of five points and the highest quintile a value of one point. The total score ranged from 7 (worst) to 35 (best), with higher score values representing greater adherence to a healthy diet. Total energy intake was measured in kilocalories (kcal) according to the FFQ.

Serum samples used to characterise the participants were collected and frozen at -20 °C and stored at -70 °C. Cotinine concentrations were determined by a modified method of the Nicotine Metabolite RIA kit (Diagnostic Products Corporation, LA, USA). For cotinine a cut-off point of 100 µg/L or over was used to separate smokers from non-smokers. The level of sensitive C reactive protein (sCRP) was determined using a chemiluminescent immunometric assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA).

In Health 2000, Vitalograph bellow spirometers (Vitalograph Ltd., Buckingham, England) were used, while in Health 2011 the Medikro® SpiroStar flow-volume spirometer and Medikro® Spiro2000 software, was used. To ensure comparability between the measurements a validation study was performed, which showed no significant difference between the two devices [24]. The spirometers were calibrated with a one-litre calibration pump, and the equipment was checked every morning before the measurements. The measurements were made by specially trained laboratory technicians following standard guidelines and instructions. The technicians demonstrated the test procedure to all subjects individually. When the subject had learned the technique and rehearsed it once or twice, the aim was to produce at least two as consistent curves as possible. For forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) the technician instructed the subjects to fill their lungs with air and then to exhale as forcefully and completely as possible, urging them towards the end of the test. Failed efforts and those with questionable performance due to fatigue, or otherwise poor co-operation were excluded from the analysis. The quotient FEV₁/FVC

145 was calculated using the highest readings of FEV₁ and FVC from technically acceptable efforts
146 recorded in BTPS (body temperature and pressure, saturated with water vapour) values. FEV₁/FVC
147 below the lower limit of normal (< LLN) was considered to indicate airway obstruction.
148 Bronchodilation was not performed for all subjects. The individual results were computed on the
149 basis of the GLI reference values [6] for corresponding age, sex and height were used. Development
150 of a new airway obstruction was analysed from the spirometry performed in Health 2011.

151 Health 2000 study was approved by the Ethics Committee for Epidemiology and Public Health in
152 the Hospital District of Helsinki and Uusimaa and Health 2011 in the Coordinating Ethics
153 Committee of the Hospital District of Helsinki and Uusimaa. All participants gave their written
154 informed consent.

155 The sampling design was accounted for in all analyses using the survey package [28, 29] of the R
156 statistical software package [R Core Team (2017). R: A language and environment for statistical
157 computing. R Foundation for Statistical Computing, Vienna, Austria. URL [https://www.R-](https://www.R-project.org/)
158 [project.org/](https://www.R-project.org/)]. The effects of oversampling of the 80-year old and older in 2000, and nonresponse in
159 the full sample were accounted for using the inverse probability weighting [30].

160 Regression analyses were based on generalised linear models. In addition to the simple regression
161 models containing the risk factors one at a time, in which only age and sex were adjusted for (model
162 1), we adjusted also for age, sex and level of education (model 2), for age, sex and smoking (model
163 3), for age, sex, level of education and smoking (model 4) and also a fully adjusted multiple
164 regression model containing all aforementioned risk factors (model 5) was analysed. Crude
165 incidence rates and their 95% confidence intervals were calculated per 1000 person years.

166

167 **Results**

168 There were altogether 3863 subjects, 1651 (42.7%) males and 2212 (57.3%) females, with normal
169 spirometry during the first survey and a re-performed spirometry 11 years later. Baseline
170 characteristics in the study population including demographics, physical examinations, tested
171 laboratory values and patient reported outcomes at baseline are described in Table 1. The
172 prevalence of nonresponders who participated in Health 2000 but not in Health 2011 was biggest in
173 subjects aged 65–100 in Health 2000.

174 New cases of airway obstruction occurred in 124 subjects, with a cumulative 11-year incidence of
175 3.2% corresponding to an incidence rate of 5.6/1000 person-years (PY) (95% CI 3.8–5.6) (Table 2).
176 The incidence rate of males was higher (6.3/1000PY, 95% CI 4.9–8.2) and that of females
177 (5.0/1000PY, 95% CI 3.9–6.6). The highest incidence rate, 9.9/1000PY (95% CI 4.8–16.7), was in
178 the age group of 65–100 years.

179 The development of airway obstruction associated in fully adjusted multiple regression model with
180 current smoking, previously diagnosed asthma, increasing sCRP and decreasing AHEI index, and of
181 these current smoking and previously diagnosed asthma were the strongest risks for airway
182 obstruction (Table 1). In basic model with age and sex adjustment development of airway
183 obstruction associated also with low physical activity, chronic bronchitis, decreasing BMI and waist
184 circumference, and additionally, decreasing AHEI index meaning healthy diet protected from
185 airway obstruction whereas the total energy intake did not have an effect. Cotinine had no
186 association with airway obstruction in fully adjusted model (not reported). Cotinine and self-
187 reported smoking are indicators of same phenomenon taking power in analysis from each other,
188 though cotinine ≥ 100 $\mu\text{g/mL}$ had an association with airway obstruction in other models (Table 1).

189

190 Discussion

191 In this study the incidence of airway obstruction based on spirometry (FEV_1/FVC below the lower
192 limit of normal) was evaluated in a population based cohort (age > 30 years of age) with a follow-
193 up of 11 years. The overall incidence rate was 5.6/1000 PY, 6.3/1000 PY for males and 5.0/1000
194 PY for females. The main determinants for the development of airway obstruction were current
195 smoking, previously diagnosed asthma, increased sCRP and low AHEI index.

196 In previous studies the incidence rates of COPD have varied from 2.6–16.0 per 1000 PY [4,5,7-12].
197 The wide variation can be at least partially explained by differences in study approaches. When the
198 incidence rates are based on retrospective health registries, such as given diagnoses, hospital
199 admission data or use of medication, the data is highly dependent on the probability of a patient
200 seeking for medical help, the diagnostic practices of different kind of health-care facilities as well as
201 the coverage of register data. Studies evaluating self-reported physician-diagnosed COPD,
202 symptoms or medications indicative of COPD are dependent on the participants' understanding on
203 his or her health.

204 When the estimates are based on spirometry data, it is possible to find also the undiagnosed cases.
205 Spirometry based incidence studies are also more comparable to each other, even though the
206 definition of the cut-off value for airway obstruction can vary. Fixed FEV_1/FVC –ratio used
207 frequently in many epidemiological studies is naturally lower in tall subjects and reduces with
208 normal ageing. In the present study we used the lower limit of normal (LLN) which is individually
209 predicted to determine airway obstruction in comparison to age and body size match healthy, non-
210 smoking population. These estimates do not cause age or size related bias in the results. In the
211 Rotterdam Study, the pre-bronchodilator $FEV_1/FVC < 0.70$ or in the absence of spirometry, COPD
212 diagnosis verified from medical records, resulted in an incidence rate of 8.9/1000 PY. Based on
213 spirometry data alone the incidence rate of 11.7/1000 PY was observed with fixed ratio and much
214 lower incidence of 5.2/1000PY with LLN criteria [7]. This was in line with our results. In the

215 Netherlands, however smoking was more prevalent. Only 35% of subjects were non-smokers,
216 compared to 53% in the Finnish population [7].

217 Current smoking and previous diagnosis of asthma associated independently to incident airway
218 obstruction, both well recognised risk factors of COPD [2]. Smoking had decreased in the Health
219 2000 survey significantly during the follow-up time of 11 years, among the men in all age cohorts
220 and among the women in age cohorts of 30–54 years [23]. The earlier finding of an association
221 between sCRP and COPD was also confirmed in this study [16].

222 The protective effect of a healthy diet has been under recent research interest. In this study, an
223 inverse association between AHEI index and incident, spirometry based airway obstruction was
224 observed. The association remained significant in all models performed which means healthy diet
225 protected from airway obstruction regardless of energy intake. High AHEI index reflects the
226 protective effect of high intakes of whole grains, polyunsaturated fatty acids, nuts and long chain
227 omega-3 fats and low intakes of red/processed meats, refined grains and sugar sweetened drinks.
228 Earlier studies have reported that high fruit and vegetable consumption [20] and more-frequent fish
229 intake [26, 31] can protect from the disease. AHEI score has been studied in clinical COPD only
230 once and an inverse association between higher AHEI score and the incidence of COPD was
231 observed [21]. In this large prospective study diagnosis of COPD was based on self-reported
232 questionnaire. As a validation study, a random sample of medical records of the participants were
233 assessed. In 71% of the COPD cases spirometry was available confirming the self-reported COPD
234 [21].

235 In addition to COPD, chronic bronchitis is a symptom of multiple other conditions [32]. Therefore,
236 our result about chronic bronchitis having association with new airway obstruction only in age and
237 sex adjusted model is rational. In BOLD study 129 (11%) subjects had both chronic bronchitis and

238 COPD [32], while we found that 9 (7.6%) of those with new obstruction reported symptoms of
239 chronic bronchitis; these results being comparable.

240 A limitation in our study is that bronchodilation test was not performed for all, and therefore, we
241 could not separate reversible and non-reversible airway obstruction. However, our study population
242 was aged 30 and over at baseline and only 14 subjects (11.2%, Table 1) with new airway
243 obstruction reported to have asthma in Health 2011, and therefore apparently most of these with
244 new airway obstruction are COPD [33]. Values of the risk factors, such as smoking status, sCRP
245 and AHEI index, might have changed during follow-up and have some effect on our results, but as
246 our objective was to assess the potential predictors of obstruction incidence we did not evaluate the
247 associations of risk factor changes during the follow-up and the obstruction incidence. Furthermore,
248 these associations are likely to operate in two directions as, for example, weight changes according
249 to the lifestyle factors (daily energy intake and physical activity). Additionally, we had no data
250 about smoked pack-years and respiratory medications used in pulmonary diseases. The follow-up
251 time of 11 years might be, especially, in the younger age groups too short for the development of
252 airway obstruction, and correspondingly, in older age groups too long. Additionally, the prevalence
253 of nonresponders was biggest in the oldest age group, aged 65–100 in Health 2000 and 76 or older
254 in Health 2011, where the physical fragility probably affected why these subjects performed not
255 spirometry or participated in Health 2011 at all, however, this was accounted for in analyses by
256 inverse probability weighting.

257

258 **Conclusions**

259 Using the similar study approach our findings on the incidence of airway obstruction are in line
260 with the previously published figures in Europe. Our study nicely completed the previous findings

261 and further addressed the importance of healthy diet as an independent risk factor for the
262 development of airway obstruction.

263

264 The authors report no conflicts of interest.

265

266 **References**

- 267 1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional,
268 and national incidence, prevalence, and years lived with disability for 310 diseases and
269 injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.
270 Lancet. 2016; 388 (10053): 1545-602.
- 271 2. Fletcher C, Peto R. The natural history of chronic airflow obstruction. BMJ. 1977;
272 1(6077):1645-8.
- 273 3. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic , Sridhar
274 D, Campbell H, Chan KY, Sheikh A, Rudan I; Global Health Epidemiology Reference
275 Group (GHERG). Global and regional estimates of COPD prevalence: Systematic review
276 and meta-analysis. J Glob Health. 2015; 5(2): 020415.
- 277 4. Afonso ASM, Verhamme KMC, Sturkenboom MCJM, Bruselle GGO. COPD in the general
278 population: prevalence, incidence and survival. Resp Med. 2011 (105): 1872-84.
- 279 5. Garcia Rodriguez LA, Wallander MA, Tolosa LB, Johansson S. Chronic obstructive
280 pulmonary disease in UK primary care: incidence and risk factors. COPD. 2009; 6 (5): 369-
281 79.
- 282 6. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson
283 JL, Ip MSM, Zheng J, Stocks J and the ERS Global Lung Function Initiative. ERS Task

- Force. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40 (6): 1324-1343.
7. Terzikhan N, Verhamme KMC, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smoker and non-smokers: the Rotterdam study. *Eur J Epidemiol.* 2016; 31 (8): 785-92.
8. Van Durme YM, Verhamme KM, Stijnen T, Van Rooij FJA, Van Pottelberge GR, Hofman A, Joos GF, Stricker BHC, Brusselle GG. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. *Chest.* 2009; 135 (2): 368-77.
9. Kojima S, Sakakibara H, Motani S, Hirose K, Mizuno F, Ochiai M, Hashimoto S. Incidence of chronic obstructive pulmonary disease, and the relationship between age and smoking in a Japanese population. *J Epidemiol* 2007; 17(2): 54-60.
10. De Marco R, Accordini S, Cerveri I, Corsico A, Antó JM, Künzli N, Janson C, Sunyer J, Jarvis D, Chinn S, Vermeire P, Svanes C, Ackermann-Liebrich U, Gislason T, Heinrich J, Leynaert B, Neukirch F, Schouten JP, Wjst M, Burney P. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med.* 2007; 175 (1):32-9.
11. Lindberg A, Eriksson B, Larsson L-G, Rönmark E, Sandström T, Lundbäck B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. *Chest.* 2006; 129 (4):879-85.
12. Johannessen A, Omenaas E, Bakke P, Gulsvik A. Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population. *Int J Tuberc Lung Dis.* 2005; 9 (8): 926-32.
13. Johannessen A, Eagan TM, Omenaas ER, Bakke PS; Gulsvik A. Socioeconomic risk factors for lung function decline in a general population. *Eur Respir J.* 2010; 36 (3): 480-7.

14. Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux PO, Curjuric I, Kromhout H, Rochat T, Rothe T, Russi EW, Schikowski T, Schindler C, Schwartz J, Turk A, Vermeulen R, Probst-Hensch N, Künzli N; SAPALDIA team. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss cohort study on air pollution and lung and heart diseases in adults. *Am J Respir Crit Care Med*. 2012; 185 (12): 1292-300.
15. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest*. 2009; 135 (1): 173-80.
16. Agassandian M, Shurin G, Ma Y, Shurin MR. C-reactive protein and lung diseases. *Int J Biochem Cell Biol*. 2014; 53: 77-88.
17. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest*. 2005; 128 (66): 3792-8.
18. Kunisaki KM, Niewoehner DE, Singh RJ, Connett JE. Vitamin D status and longitudinal function decline in the Lung Health Study. *Eur Respir J*. 2011; 37 (2): 238-43.
19. Okubo H, Shaheen SO, Nitani G, Jameson KA, Syddall HE, Sayer AA, Dennison EM, Cooper C, Robinson SM; Hertfordshire Cohort Study Group. Processed meat consumption and lung function: modification by antioxidants and smoking. *Eur Respir J*. 2014; 43 (4): 972-82.
20. Kaluza J, Larsson SC, Orsini N, Linden A, Wolk A. Fruit and vegetable consumption and risk of COPD: a prospective cohort study of men. *Thorax*. 2017; 72 (6): 500-9.
21. Varraso R, Chiuve SE, Fung TT, Barr RG, Hu FB, Willett WC, Camargo CA. Alternate Healthy Eating Index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study. *BMJ*. 2015; 350: h286.

22. Kainu A, Pallasaho P, Pietinalho A. No change in prevalence of symptoms of COPD between 1996 and 2006 in Finnish adults – a report from the FinEsS Helsinki Study. *Eur Clin Respir J* 2016; 3: 31780.
23. Koskinen S, Lundqvist A, Ristiluoma N, eds. Health, functional capacity and welfare in Finland in 2011. National Institute for Health and Welfare (THL), Report 68/2012. Helsinki 2012. ISBN 978-952-245-769-1.
24. Heistaro S. (ed), Methodology report. Health 2000 Survey. Publications of the National Public Health Institute B 26/2008. National Public Health Institute, Helsinki, Finland 2008, ISBN 978-951-740-860-8 (pdf), <http://www.terveys2000.fi>.
25. Männistö S, et al. Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. *J Clin Epidemiol.* 1996; 49:401-9.
26. Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, Pietinen P. Validity of a food frequency questionnaire varied by age and body mass index. *J Clin Epidemiol.* 2006 Sep;59(9):994-1001.
27. McCullough ML, Feskanich D, Stampfer MJ, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. *Am J Clin Nutr.* 2002;76: 1261–71
28. Lumley T. Analysis of complex survey samples. *J Stat Software.* 2004; 9(1): 1-19.
29. Lumley T. Survey: analysis of complex survey samples. 2016. R package version 3.31-5.
30. Härkänen T, Karvanen J, Tolonen H, Lehtonen R, Djerf K, Juntunen T, Koskinen S. Systematic handling of missing data in complex study designs - experiences from the Health 2000 and 2011 Surveys. *Journal of Applied Statistics.* 2016; 43 (15): 2772-90.
31. Varraso R, Barr RG, Willett WC, Speizer FE, Camargo CA Jr. Fish intake and risk of chronic obstructive pulmonary disease in 2 large US cohorts. *Am J Clin Nutr.* 2015; 101 (2): 354-61.

- 357 32. Mejza F, Gnatiuc L, Buist AS, Vollmer WM, Lamprecht B, Obaseki DO, Nastalek
358 P, Nizankowska-Mogilnicka E, Burney PGJ; BOLD collaborators; BOLD study
359 collaborators. Prevalence and burden of chronic bronchitis symptoms: results from the
360 BOLD study. Eur Respir J. 2017; 22;50(5).
- 361 33. GINA Report, Global strategy for asthma Management and Prevention. Available at:
362 [https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-](https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/)
363 [prevention/](https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/). Last accessed 27.11.2018.